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Sildenafil, a novel effective oral therapy for male erectile dysfunction

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Objectives To determine the efficacy and safety of sildenafil, a novel orally active inhibitor of the type-V cyclic guanosine monophosphate-specific phosphodiesterase (the predominant isoenzyme in the human corpus cavernosum) on penile erectile activity in patients with male erectile dysfunction of no established organic cause.

Patients and methods Twelve patients (aged 36–63 years) with male erectile dysfunction of no established organic cause were entered into a double-blind, randomized, placebo-controlled, crossover study which was conducted in two phases. In the first phase (four-way crossover), treatment efficacy was evaluated by measurements of penile rigidity using penile plethysmography during visual sexual stimulation at different doses of sildenafil (10, 25 and 50 mg or placebo). In the second phase (two-way crossover), efficacy was assessed by a diary record of penile erectile activity after single daily doses of sildenafil (25 mg) or placebo for 7 days.

Results The mean (95% confidence interval, CI) duration of rigidity of >80% at the base of the penis was 1.3 min (0.4–3.1) in patients on placebo, 3.5 min (1.6–7.3; $P = 0.009$) on 10 mg, 8.0 min (3.7–16.7; $P = 0.003$) on 25 mg and 11.2 min (5.6–22.3; $P < 0.001$) on 50 mg of sildenafil. The mean (95% CI) duration of rigidity of >80% at the tip of the penis was 1.2 min (0.4–2.7) on placebo and 7.4 min (2.4–8.5; $P=0.001$) on 50 mg sildenafil. From the diary record of daily erectile activity, the mean (95% CI) total number of erections was significantly higher in patients receiving sildenafil was 6.1 (3.2–11.4), compared with 1.3 (0.5–2.7) in those on placebo; 10 of 12 patients reported improved erectile activity while receiving sildenafil, compared with two of 12 on placebo ($P= 0.018$). Six patients on active treatment and five on placebo reported mild and transient adverse events which included headache, dyspepsia and pelvic musculo-skeletal pain.

Conclusion These results show that sildenafil is a well tolerated and effective oral therapy for male erectile dysfunction with no established organic cause and may represent a new class of peripherally acting drug for the treatment of this condition.

Keywords Sildenafil, penile erection, penile plethysmography

Introduction

Male erectile dysfunction has been defined as the inability to attain and/or maintain penile erection sufficient for satisfactory sexual performance [1]. Nearly half a century ago, Kinsey *et al.* recognized that male erectile dysfunction was a common disorder [2]. A recent and extensive population-based survey confirmed the high prevalence of this disorder, with an estimated prevalence across all ages of 10%, rising to 52% in men aged between 50 and 70 years [3]. Male erectile dysfunction is generally accepted to affect adversely the quality of life and there is evidence to indicate that it is frequently associated with depression, increased anxiety and poor self-esteem in affected patients [1,4]. Although male erectile dysfunction represents a major clinical problem, medical therapy for this condition remains unsatisfactory because it is invasive or ineffective.

Recent studies that have examined the mechanism of penile erection have indicated that relaxation of the corpus cavernosal smooth muscle cells, which is mediated by both non-adrenergic, non-cholinergic neurons and by cholinergic mechanisms, is caused by nitric oxide and its second messenger, cyclic guanosine monophosphate (cGMP) [5,6]. Sildenafil is a potent and competitive inhibitor of the type-V cGMP-specific phosphodiesterase enzyme, the predominant isoenzyme in the human corpus cavernosum. As such, sildenafil may be expected to enhance relaxation of the corpus cavernosal smooth muscle, which in turn increases blood flow into the cavernosal spaces, thus leading to increased intracavernosal pressure, a key factor in producing an erect penis [7,8].

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This study was designed to determine if sildenafil administered orally in single doses effectively improved penile erections in patients with erectile dysfunction for which there was no established organic cause, and to evaluate the safety of sildenafil in such patients.

Patients and methods

The study was approved by the local ethics review committee. The study comprised out-patients who were referred for the treatment of male erectile dysfunction and these were included if they were aged 18–70 years and had penile erectile dysfunction of at least 6 months' duration for which there was no established organic cause on clinical evaluation and blood tests. Patients were excluded from the study if they suffered from diabetes mellitus, hypertension or alcohol abuse. Twelve patients entered the study (mean age 47.9 years, range 36–63) with a mean duration of penile erectile dysfunction of 3.4 years (range 1.5–10). None of the patients had received other treatment for male erectile dysfunction for at least 2 weeks before the start of or throughout the study.

The study was conducted in two phases; the initial phase was a double-blind, placebo-controlled, four-way crossover trial with a 'washout' period of at least 3 days allowed between consecutive treatment periods, an interval which was considered adequate to ensure clearance of sildenafil from the circulation. During each treatment period, patients were admitted to a private hospital bed and received a single dose of sildenafil (10, 25 or 50 mg) or placebo. Each dose was followed by visual sexual stimulation which started 30 min after dosing and continued for 2 h. For visual sexual stimulation, patients were allowed to choose from a selection of sexually explicit videotapes and magazines. Drug efficacy was evaluated by the measurement of penile rigidity, during periods of tumescence, at the base and tip of the penis using penile plethysmography (RigiScan, Dacomed Corporation, Minneapolis, USA). Tumescence was recorded continuously from 30 min before dosing to 2.5 h afterwards [9,10].

The second phase of the study consisted of a double-blind, randomized, placebo-controlled two-way crossover study in which the patients from the first phase received single daily doses of sildenafil (25 mg) or placebo for 7 days. There was a washout period of at least 3 days between the phases of the study and one of at least 7 days between the treatment periods of the second phase. During each treatment period, patients were instructed to take the daily dose of sildenafil or placebo 1–2 h before they were most likely to have an opportunity for sexual activity. Patients were provided with a diary and instructed to keep a record of their erectile activity and to grade their erections on a scale of 1–4 (Table 1). At the end of each treatment period, patients were asked for an overall assessment of treatment efficacy by recording their response to the question: 'Do you feel that the treatment over the past seven days has improved your erections?' Adverse events were recorded at each visit and laboratory blood and urine tests were monitored throughout the study.

The key variable derived from the RigiScan output was the duration of penile rigidity $>80\%$ at the base and tip of the penis. Only penile erections which started during the 2 h of visual sexual stimulation were included in the analysis. If more than one event was recorded, the durations were summed. Results were assessed using an ANOVA appropriate for a four-treatment, four-way crossover design. In the second phase of the study, an adequate response was defined as a grade 3 or 4 erection. The total number of grade 3 and 4 erections during each 7-day treatment period derived from the diary record were assessed by an ANOVA appropriate to a two-period, two-way crossover study. The overall assessment by the patients of the effects of treatment on penile erectile activity at the end of each treatment period were analysed using Mainland-Grant's test for treatment and period effects, and the Altman method was used to test for a treatment effect × period interaction [11,12]. The data were expressed as the geometric mean and 95% CI; values of $P < 0.05$ were considered to indicate significant differences.

Results

All 12 patients completed both phases of the study. Four patients had received previous intracavernosal papaverine for erectile dysfunction, with three having a full rigid erection and one having a weak response to this therapy. The other eight patients were previously untreated.

Penile plethysmography

One subject had an erection during the treatment period when he received 25 mg of sildenafil which started before visual sexual stimulation and continued through-

Table 1 Grading of penile erectile response

Grade	*Description of erection*
1	Increase in size of penis but no hardness
2	Increase in size and slight increase in hardness (rigidity), but insufficient for sexual intercourse
3	Increase in hardness (rigidity) sufficient for sexual intercourse, but not fully rigid
4	Fully rigid erection

out the treatment period. As this response provided no information on the effect of treatment, this observation was excluded from the analysis. Penile plethysmography from another patient was not recorded (for technical reasons) when he received placebo and was therefore excluded from the analysis.

The duration of a rigidity of >80% at the base and tip of the penis during visual sexual stimulation was significantly higher in each treatment group compared to placebo (Fig. 1). The onset of penile tumescence occurred within 10 min of commencing visual sexual stimulation or within about 40 min of dosing with sildenafil. There was no evidence of a carry-over effect for any variable in the first phase of the study.

Diary of daily erectile activity

The records from the second phase of the study were complete for the 12 patients from the two treatment periods. All patients took their medication between 20.00 hours and 23.00 hours. The mean (95% CI) total number of erections summed from both treatment periods in patients receiving sildenafil was 6.1 (3.2–11.4), significantly higher than the 1.3 (0.5–2.7) for those receiving placebo ($P=0.005$). However, there was evidence of a 'sequence effect' for the total number of erections ($P= 0.059$): the mean (95% CI) number of erections was higher in patients who received placebo followed by sildenafil (10.1; 1.3–13.3) compared with those who received sildenafil before placebo (3.6; 1.0–10.9).

The ratio of the number of erections on sildenafil and placebo was determined separately in the two sequence groups and was 4.1 in those who received placebo in the first treatment period, compared with 3.3 in those who received sildenafil followed by placebo. Because there was a marked increase in the number of erections on sildenafil compared to placebo in both sequences (Table 2), it was considered appropriate to combine both sequences for estimating statistical differences.

The relationship between the number of grade 3 and 4 erections over each 7-day treatment period and the time of dosing (up to 12 h after receiving the dose) is shown in Fig. 2. The mean number of erections in the 2 h after dosing was significantly higher with sildenafil (1.6) compared with placebo (0.3). In contrast, there was no difference between the treatments after the first 2 h. The peaks between 8 and 10 h after dosing correspond to early morning erections.

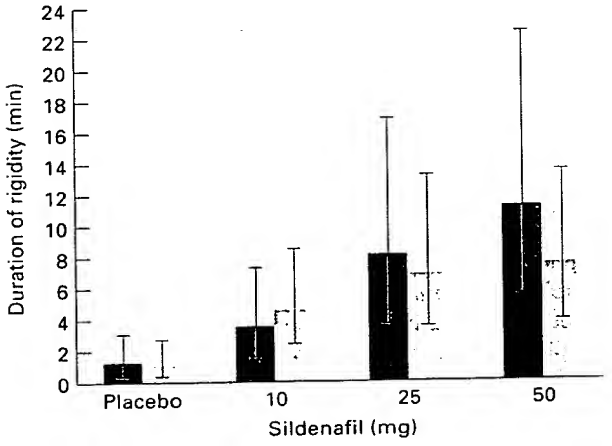

Fig. 1. The mean (95% CI) duration of rigidity at the base (green) and tip (red) of the penis in patients receiving placebo or different doses of sildenafil. Differences from placebo were significant at the base for 10 mg ($P = 0.009$), 25 mg ($P = 0.003$) and 50 mg ($P < 0.001$) and at the tip for 10 mg and 50 mg ($P = 0.001$) and 25 mg ($P = 0.002$).

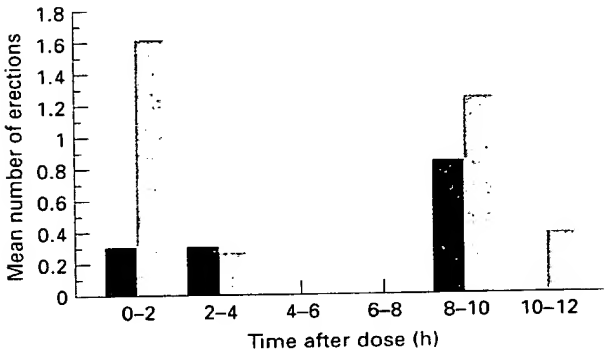

Fig. 2. The mean number of grade 3 and 4 erections, as recorded in the patients' diaries, with time after single doses of sildenafil (red) or placebo (green 2).

Table 2 Number of grade 3 and 4 erections after sildenafil (25 mg) and placebo daily for 7 days

Sequence group	*Ratio of sildenafil to placebo (95% CI)*	P
Placebo then sildenafil	4.1 (1.3–13.3)	
Sildenafil then placebo	3.3 (1.0–10.9)	
Combined sequence groups	3.7 (1.6–8.5)	0.006

Patients' overall assessment of treatment on erectile activity

There was no evidence of a treatment period effect or a treatment × period interaction. There was a statistically significant improvement of erectile activity on sildenafil: 10 of 12 patients reported improved erectile activity with sildenafil compared with only two of 12 receiving placebo ($P = 0.018$).

Adverse events

In the first phase of the study, two patients at each dose reported headache after taking 50 mg and 25 mg of sildenafil. One patient who received 50 mg also reported backache. In the second phase, six of 12 patients taking sildenafil and five of 12 on placebo reported adverse events which included headache, dyspepsia and pelvic musculo-skeletal pain. Except in one patient who complained of severe headache on sildenafil, in all other cases the adverse events were mild and transient. There were no significant changes in pulse rate, blood pressure or laboratory safety data.

Discussion

This study shows that sildenafil, administered in single oral doses, is effective in improving erectile activity in patients with male erectile dysfunction for which there is no established organic cause. There was an improvement in erectile activity, measured objectively by RigiScan monitoring and subjectively when assessed by the patient in his home environment using a diary of erectile activity.

Although a wide range of oral therapy, including folk remedies, is used in the treatment of male erectile dysfunction, most have not been tested in rigorous clinical studies. Of the currently available oral therapies for male erectile dysfunction, the α2-adrenergic blocking agent, yohimbine hydrochloride, has been studied most widely; it is believed to exert its beneficial effects on erectile activity by central mechanisms on the nervous system [13]. Well-controlled double-blind studies with this compound have shown that it has only limited efficacy on erectile function when used singly or in combination with methyltestosterone and a variety of vitamins and caffeine-based stimulants [14,15]. Injection of vasodilator agents directly into the corpora cavernosa has developed rapidly as a therapy for male erectile dysfunction of various aetiologies since the technique was first introduced in 1982 [16]. The agents commonly used include papaverine, phentolamine and PGE1, which have been used singly or in combination. They improve erectile activity by producing relaxation of the smooth muscle of the corpus cavernosum and of the cavernosal arteries. Although this form of therapy is effective, it is invasive and is associated with a high rate of withdrawal from treatment which, in one series, was 41% at the 12 month follow-up [17]. Other major disadvantages of intracavernosal injection therapy are priapism, penile pain and penile corporal fibrosis with chronic use [17–19]. In the present study, sildenafil was well tolerated when administered in single oral doses. Although six of 12 patients reported headaches or dyspepsia when they received single daily doses of sildenafil, these adverse events were mild and transient in most cases. These adverse events may be related to the effects of sildenafil on the smooth muscle in the vasculature and upper gastro-intestinal tract.

Penile rigidity is the most important determinant of the quality of an erection. In the first phase of the study, an adequate response was defined as the achievement of rigidity of $\geqslant 80\%$ at the base and tip of the penis, based on published evidence that suggested a penile rigidity of $\geqslant 70\%$ was adequate for sexual intercourse [20,21]. Because sildenafil is believed to exert its beneficial effects by inhibiting the phosphodiesterase type-V enzyme and, therefore, increasing the intracellular levels of cGMP in the corporal smooth muscle, it would not be expected to produce an erectile response when used in the absence of a drive on the nitric oxide-cGMP pathway. This drive can be provided by physiological mechanisms that can be initiated by visual or other forms of sexual stimulation.

The efficacy of sildenafil in improving erectile activity was confirmed in the second phase of the study when patients received the compound daily at home. The sequence effect observed in this phase of the study is not explained by a difference in age or duration of erectile dysfunction between the sequence groups but may be explicable by an imbalance in the treatment groups; the number and quality of penile erections at baseline tended to be lower in the group who received sildenafil followed by placebo than those who received placebo first. In this study, the frequency of sexual intercourse was not measured as the treatment period was too short for this assessment.

In conclusion, sildenafil is a well-tolerated and effective oral therapy in patients with erectile dysfunction. It may represent a new class of peripherally acting drug with great potential in this condition. Studies are underway to assess the long-term safety and efficacy of sildenafil.

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